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Synthetic Route for Racemic Synthesis of *Trans*-(1R,S, 3R,S)-2-methylene-1,3-dithiane-1,3-dioxide and Reactivity with N-carbethoxy-1,2-dihydropyridine as a Dienophile

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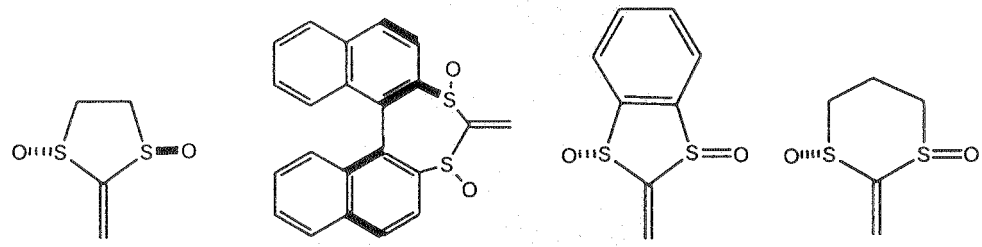
Trans-(1R,S, 3R,S)-2-methylene-1,3-dithiane-1,3-dioxide has been prepared in 22% yield in three steps and cycloaddition of (**4a**) with N-carbethoxy-1,2-dihydropyridine gave a moderate diastereoselective (76 : 24) in 20% yield. All the major compounds (**4b**) and (**7a**) were determined by X-ray analysis.

Key Words: Chiral ketene equivalents, [4+2] Cycloaddition, 1,3-Dithiane, Bicyclic ketones.

INTRODUCTION

Cyclic and bicyclic ketones are important intermediates in organic synthesis. Ketene equivalents have found widespread use as important reagents in Diels-Alder reactions for the synthesis of cyclic, fused and bridged unsaturated ketones[1]. Sulfur containing chiral ketene equivalents are extremely useful synthons in asymmetric synthesis. The cyclic alkenyl sulfoxide C_2-symmetric ketene equivalents (**1–4**) have been developed by Aggarwal *et al.*[2–5] and found to be highly effective dienophiles in Diels-Alder reactions with a range of dienes (**Scheme-1**). The advantage of this chiral ketene equivalent is that it requires only two steps for removal of chiral auxiliary from cycloadduct[4].



(1) (2) (3) (4)

Scheme-1

In this paper we have describe full details of the preparation of the racemic synthesis of *trans*-(1R,S, 3R,S)-2-methylene-1,3-dithiane-1,3-dioxide (**4a**) and Diels-Alder reaction of (**4a**) with N-carboethoxy-1,2-dihydropyridine are also described. Recemic (**4a**) was synthesized by reported method[5]. Racemic (**4a**) was readily prepared in three steps as outline in **Scheme-2**. Commercially available

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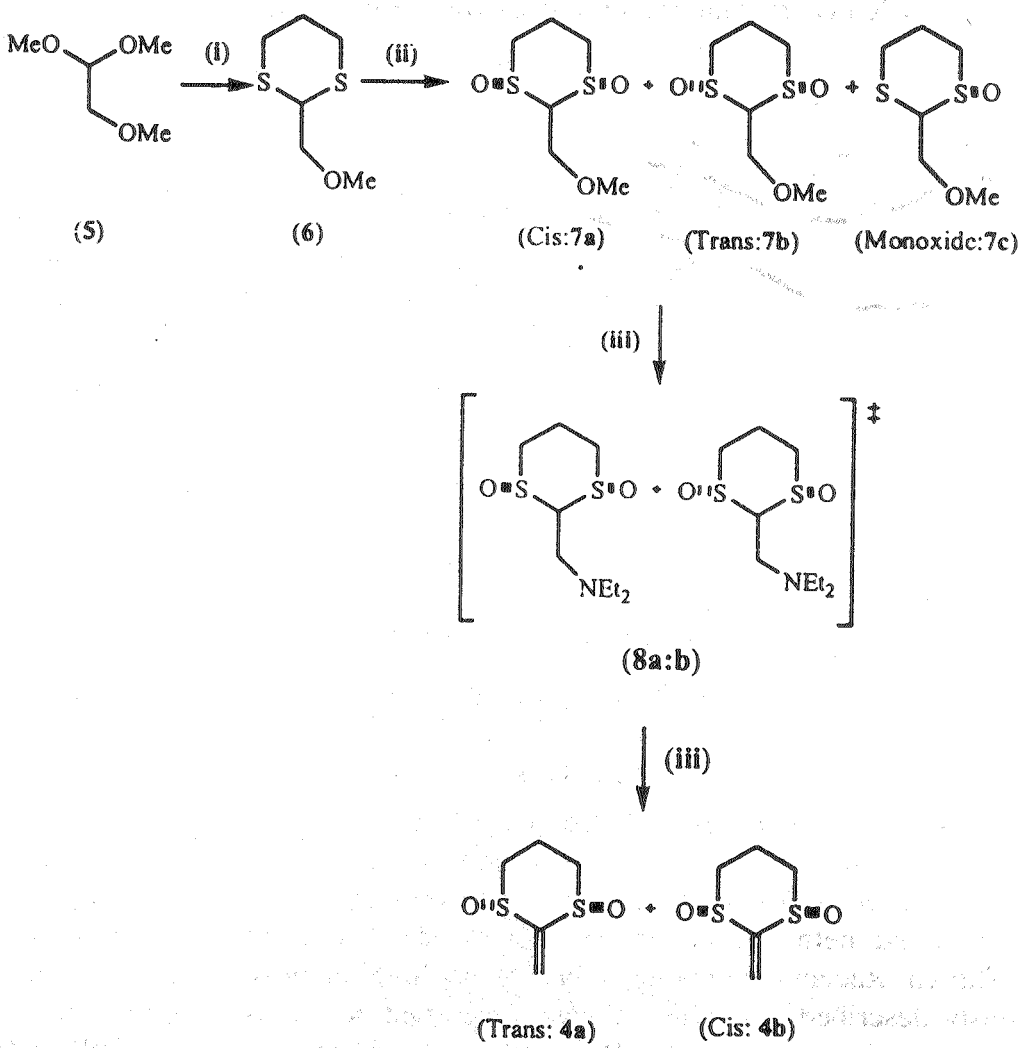
acetal (**5**) with propanedithiol under acid catalysis gave the methoxymethyl-1,3-dithiane (**6**) in 94% yield. Racemic oxidation of dithiane (**6**) with *m*-CPBA in Et_2O gave exclusively the *cis*-bis-sulfoxide (**7a**) with *trans* -bis-sulfoxide (**7b**) in the ratio 72 : 28. Fortunately the monoxide (**7c**) is easily separable from the *cis* : *trans* (**7a : 7b**) but separations of the *cis* : *trans* (**7a : 7b**) are more difficult by crystallization or by column chromatography and high *cis* ratio is desirable. Sodium periodate oxidation is shown highly *cis* selective (ratio: 72 : 28) but work up is difficult and after 48 d it gave exclusively monoxide (**7c**) in 60% yield with low yield of *cis* : *trans* (**7a : 7b**) (7% yield). Compound (**7a : 7b**) converted to the diethyl and dimethylamino derivatives in acetonitrile at room temperature and refluxing in acetonitrile there is no formation of intermediate compound (**8a : 8b**) in both temperatures. We got directly the elimination product *cis* : *trans* (**4a : 4b**) in 73% yield. The *cis* : *trans* (**4a : 4b**) easily purified column chromatograpy and gave two

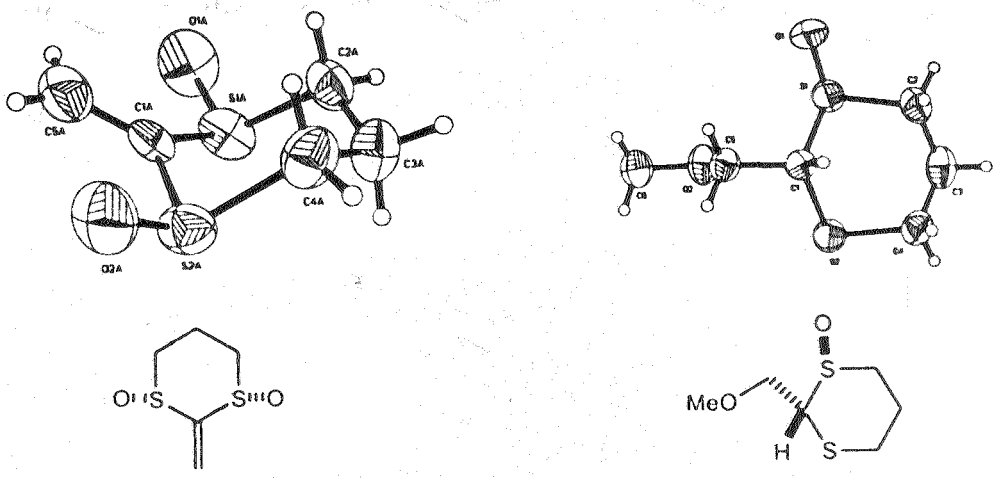


Scheme-2

Reagents and conditions: (i) $HSCH_2CH_2CH_2SH$, concentrated HCl, room temperature, 6 h (94%); (ii) (1) *m*-CPBA, Et_2O, 0°C, 2 h (*cis* : *trans*: (**7a : b**) 72 : 28; 80%, monoxide **7c** 9%);(2) $NaIO_4$, room temperature, 48 h (*cis* : *trans*: 72 : 28; 7% and monoxide 60%); (iii) Et_2NH, CH_3CN, reflux, 12 d, cis : trans (73% in ratio 85 : 15)

diastereometric products (**4a : 4b**) in 85 : 15 ratio (ratios were determined by ^{1}H NMR ($CDCl_3$) integration of crude mixture, **Scheme-2**). This shows that the elimination of *trans* dioxide **7b** could be much slower than *cis* dioxide **7a**. Therefore the *cis-meso* product **4b** was obtained in high ratio.

Diels-Alder reaction of the *trans*-[(1R,S,3R,S)-2-methylene-1,3-dithiane-1,3-dioxide (**4a**) with N-carbethoxy-1,2-dihydropyridine (**9a**) was investigated. N-Carbethoxy-1,2-dihydropyridine (**9a**) was prepared by reported method[6] in 18% yield. N-Carbethoxy-1,4-dihydropyridine (**9b**) is the side product in this reaction. We tried to separate both 1,2 and 1,4-isomers (**9a : 9b**) by column chromatography but could not separate successfully; we therefore used the 72 : 28 mixture of isomers (**9a : 9b**) in Diels-Alder reaction with dienophile (**4a**). The cyclo addition of **4a** with 1,2-dihydropyridine in propionitrile at 97°C after 8 d gave two diastereoisomeric adducts (**10a : 10b**) (76 : 24) in 20% yield (**Scheme-3**). The relative stereochemistry of *cis*-dienophile (**4b**), *cis*-dioxide (**7a**) and monoxide (**7c**) were determined by X-ray crystallography and shown in Figs. 1 and 2.

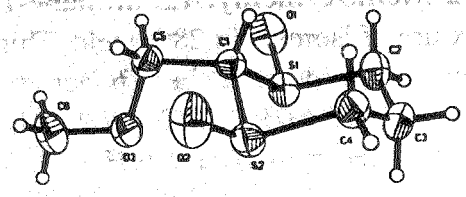


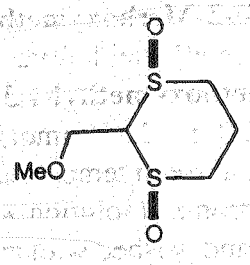
(4b) (7c)

Fig. 1

EXPERIMENTAL

m-CPBA (*meta*-chloroperoxybenzoic acid) was purified by washing an ether solution of commercially available material (Aldrich 57–86%) four times with a phosphate buffer, followed by drying and careful removal of solvent. 1,3-Propanedithiol and methyl acetaldehyde dimethyl acetal are commercially available from Aldrich. Racemic compounds **7a**, **7b** and **7c** (**Scheme-1**) were prepared as previously described[7]. All the solvents were dried before use. Proton and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX-400 high performance digital FT NMR instrument. The chemical shifts were recorded on the δ scale and were measured relative to the residual signal of chloroform at δ 7.25. All coupling constants are measured in hertz. Mass spectra was recorded by LC/MS-APCI analysis method with AGILENT 1100 MSD instrument. The ratio *cis* : *trans* (**7a : 7b**) was determined by ^{1}H NMR.





(7a)

Fig. 2

2-Methoxymethyl-1,3-dithiane (6): 1,3-Propanedithiol (7 cm^3, 67.7 mmol) and 8.4 mL concentrated hydrochloric acid were cooled to 0°C and methyl acetaldehyde dimethyl acetal (9.8 cm^3, 76.7 mmol) was added *via* syringe over 20 min. After additional 30 min, the ice bath was removed and the reaction mixture was stirred for 4.5 h at room temperature. The resulting two phase mixture was partitioned between dichloromethane (35 cm^3) and water (35 cm^3). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3×35 cm^3). The combined organic layers were washed with saturated $NaHCO_3$ (40 cm^3) and brine (40 cm^3) and then organic layer dried over $MgSO_4$. After removal of the solvent under reduced pressure the viscous, colourless residue was subjected to flash chromatography eluting with (10 : 90 acetone : pet-ether) to afford the title compound (10.3 g, 94%) as a colourless oil. $R_f = 0.95$ MeOH : EtOAc (10 : 90); δ_H (250 MHz, $CDCl_3$); 1.8–1.9 (1H, m, 5-H); 1.9–2.0 (1H, m, 5-H); 2.8 (4H, m, 4-H_2, 6-H_2); 3.32 (3H, s, OMe); 3.6 (2H, d, *J* 6.1, 7-H); 4.3 (1H, t, 2-H); δ_C 25 (C5); 38 (C4- C6); 45 (C7); 60 (C2); 75 (C-OMe); ν_{max}/cm^{-1} 2840–2880 ν(CH), 2820 ν(C-OMe).

Racemic oxidation of 2-methoxymethyl-1,3-dithiane (6) with *m*-CPBA: 2-Methoxymethyl-1,3-dithiane (4.0 g, 24.4 mmol) was dissolved in dry ether (100 cm^3) at 0°C. Purified *m*-CPBA (9.3 g, 53.7 mmol in 150 cm^3 ether) was added *via* dropping funnel over 20 min. The reaction was stirred for 2 h at 0°C, after which the white solid was collected by filtration; washing with more ether gave *cis* and *trans* dioxide together with monoxide product in 89% yield. *cis* : *trans*: **7a : 7b**: 72 : 28, ratio determined by ^1H NMR (D_2O and d_6-DMSO) integration of crude reaction mixture.

Column chromatography of the residue, eluting with EtOAc : MeOH (50 : 50), gave the *cis*-(1R,S,3R,S)-1,3-dithiane-1,3-dioxide **(7a)** as a white crystalline solid (2.5 g, 52%), m.p. = 122–125°C; $R_f = 0.26$; EtOAc : MeOH (2 : 1); δ_H (250 MHz, $CDCl_3$) 2.5 (1H, m, 5-H_a), 2.7–2.9 (2H, m, 5-H_b and 6-H_a), 3.0 (1H, m, 6H_b), 3.3 (1H, m, 4-H_a), 3.5 (3H, s, OMe), 3.51 (1H, m, 4H_b), 3.8 (1H, dd *J* 8.2 and 3.7, C*H*CH_2), 4.1–4.3 (2H, m, CHCH_2). ν_{max}/cm^{-1} 2925 ν(CH), 1029 ν(S—O). Crystal data for (**7a**) was published by Gültekin[8].

Trans*-(1R,S, 3R,S)-2-Methoxymethyl-1,3-dithiane-1,3-dioxide (7b) and *cis **7b** were obtained as mixture of isomers in 28% yield. Thin layer chromatography was used to separate *cis* : *trans* dioxide **7a : 7b** but still small amount of *cis* product **7a** was obtained. δ_H (250 MHz, $CDCl_3$) 1.9 (2H, m, 5-H_a and 5-H_b), 2.6 (2H, m, 4-H_a and 6-H_a), 3.1 (2H, m, 4-H_b and 6-H_b), 3.7 (2H, m, —CHCH_2), 4.2 (1H, m, CHCH_2).

(1R,S,2R,S) and (1R,S,2R,S)-2-Methoxymethyl-1,3-dithiane-1-oxide (7c) was obtained as a colourless solid in 9% yield. Data is shown below:

Racemic oxidation of 2-Methoxymethyl-1,3-dithiane (6) with $NaIO_4$: 2-Methoxymethyl-1,3-dithiane (2.0 g, 12.19 mmol) was dissolved in dry diethyl ether (60 cm^3) and water (10 cm^3) at room temperature. Sodium periodate (2.86 g, 13.41 mmol) was added in one portion and solution was stirred at room temperature for 48 h. The solution was filtered and washed with more hot MeOH. Solvents were evaporated under reduced pressure to give a white solid. Column chromatography of the residue, eluting with EtOAc : MeOH (90 : 10) gave (1R,S,2R,S) and (1R,S,2R,S)-2-methoxymethyl-1,3-dithiane-1-oxide **(7c)** as a white crystalline solid (1.3 g , 60%) and *cis-trans*-2-methoxymethyl-1,3-dithiane-1,3-dioxide **(7a : 7b)** in 6.57% yield.

(1R,S,2R,S) and (1R,S,2R,S)-2-methoxymethyl-1,3-dithiane-1-oxide (7c). It was obtained as a colourless solid (yield 9%) m.p. = 93–96°C; R_f = 0.87 EtOAc : MeOH (1 : 1); δ_H (250 MHz, $CDCl_3$) 2.2–2.4 (2H, m, 5-H_a and 5-H_b); 2.5–2.7 (3H, m, 4-H_a, 4-H_b and 6-H_a), 3.39 (3H, s, OMe), 3.4 (1H, d, 6-H_b), 3.7 (1H, t, CHCH_2), 3.8 (1H, dd, J 10.6 and 2.6 Hz, CHCH_2), 4.1 (1H, dd, J 10.6 and 4.3, CHCH_2). ν_{max}/cm^{-1} 2889 ν(CH); 2832 ν(C—OMe), 1030 (S—O).

Crystal data for (7c): $C_6H_{12}O_2S_2$; M = 180.28, crystallizes from ethyl acetate as colourless plates; crystal dimensions 0.50 × 0.30 × 0.15 mm. Monoclinic, a = 7.9056 (9), b = 10.1886 (14), c = 10.7845 (9) A, β = 92.362 (8)°, V = 867.92 (17) A^3, Z = 4, Dc = 1.38 Mg/m^{-3}, space group $P2_1/n$ (No. 14), Mo-Kα radiation (λ = 0.71073 A), μ = 0.556 mm^{-1}, F(000) = 384.

Three dimensional room temperature X-ray data were collected in the range 4.0° < 2θ < 60° on a Nicolet P3/F diffractometer by the Wyckoff scan method. The 2530 independent reflections (of 2694 measured) were corrected for Lorentzian polarization effects, but not for absorption. Intensity of 1803 reflection was larger then 2σ(I). The structure was solved by direct methods and refined by full matrix least squares methods on F^2 with the SHELXTL-97 program package. Hydrogen atoms were included in calculated positions and refined in riding mode. The oxygen of the sulfoxide is disordered with a ratio of 5 : 1 attached on the sulphurs *vice versa*. Refinement converged at a final R = 0.0631 (wR_2 = 0.1529 for all 2694 reflections, 149 parameters, mean and maximum δ/σ 0.000 and 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final rest-electron density –0.443 and 0.628 e A^{-3}.

Synthesis of *trans*-(1R,S,3R,S)-2-methylene-1,3-dithiane-1,3-dioxide (4a) and *cis*-(1S,R, 3R,S)-2-methylene-1,3-dithiane-1,3-dioxide (4b): *Cis* : *trans*-2-methoxymethyl-1,3-dithiane-1,3-dioxide **(7a : 7b)** (0.7 g, 3.57 mmol) was dissolved in dry acetonitrile (5 mL) at room temperature. To this solution diethylamine (5.3 mL, 51 mmol) was added. This solution was refluxed for 5 d. After 5 d the solution turned from yellow to red colour. This solution was stirred for further 7 d.

The residue was then subjected to flash chromatography eluting with (80 : 20 acetone : pet-ether) to afford the title compound:

***cis*-(1R,S, 3S,R)-2-methylene-1,3-dithiane-1,3-dioxide (4b)** was obtained as a white crystalline solid (0.37 g, 63.7%), $R_f = 0.6$. EtOAc: acetone (10 : 90); m.p. = 115–118°C; δ_H (250 MHz, $CDCl_3$) 1.83–1.98 (2H, m, 5-H_a), 2.38–2.48 (1H, m, 5-H_b), 2.62–2.71 (2H, m, 4-H_a, 6-H_a), 3.45–3.51 (2H, m, 4-H_b and 6-H_b), 6.43 (2H, s, 7-H_a and 7-H_b). ν_{max}/cm^{-1} 2926 ν(CH), 1643.01 (C═C), 1051 ν(S—O).

Crystal data for (4b): $C_5H_8O_2S_2$; M = 164.23, crystallises from EtOAc : Pet-ether as colourless plates; crystal dimensions 0.50 × 0.25 × 0.10 mm. Monoclinic, a = 12.824 (3), b = 6.7568 (18), c = 18.008 (4) A,β = 108.879 (17)°, V = 1476.4 (6) A^3, Z = 8, D_c = 1.478 Mg/m^{-3}, space group $P2_1/c$ (No. 14), Mo-Kα radiation (λ = 0.71073 A), μ = 0.646 mm^{-1}, F(000) = 688.

Three dimensional room temperature X-ray data were collected in the range $3.5° < 2\theta < 50°$ on a Nicolet P3/F diffractometer by the Wyckoff scan method. The 2589 independent reflections (of 2711 measured) were corrected for Lorentzian polarization effects, but not for absorption. Intensity of 1505 reflections was larger than 2σ(I). The structure was solved by direct methods and refined by full matrix least squares methods on F^2 with the SHELXTL-97 program package. Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final R = 0.0894 ($wR_2 = 0.1449$ for all 2589 reflections, 164 parameters, mean and maximum δ/σ 0.000 and 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final rest-electron density –0.290 and 0.332 e A^{-3}.

Trans-(1R,S,3R,S)-2-methylene-1,3-dithiane-1,3-dioxide (4a) as a yellow oil (0.13 g, 22%); $R_f = 0.3$. EtOAc : acetone (**10 : 90**). δ_H (250 MHz, $CDCl_3$) 2.7 (2H, m, 5-H_a and 5-H_b), 2.95 (2H, m, 4-H_a and 6-H_a), 3.15 (2H, m, 4-H_b and 6-H_b), 6.34 (2H, s, 7-H_a and 7-H_b). ν_{max}/cm^{-1} 2923 ν(CH), 1703 ν(C═C), 1048 ν(S═O).

N-Ethoxycarbonyl-1,2 and 1,4-dihydropyridine (9a : 9b): The title compound **9a : 9b** was prepared as previously described[7].

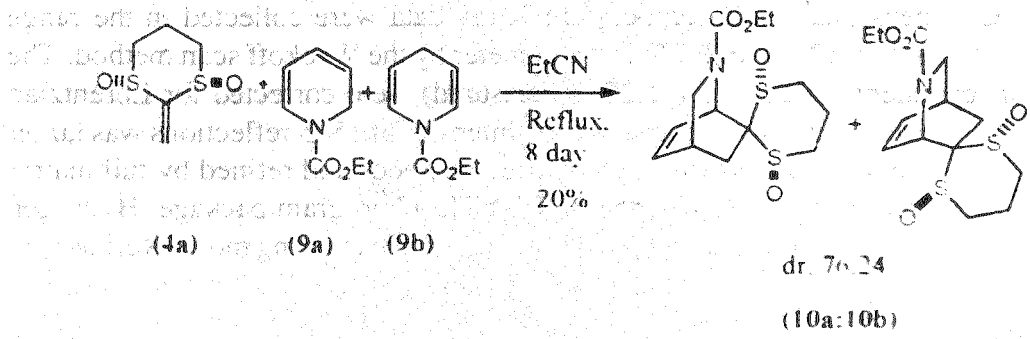
A solution of pyridine (13.4 mL, 165.8 mmol) and $NaBH_4$ (6.2 g, 165.8 mmol) in absolute ethanol (30 mL) was cooled to –50°C. Ethyl chloroformate (9 g, 82.9 mmol) in dry ether (15 mL) was added and reaction mixture were stirred further for 2 h at –50°C. The mixture was added to ice-water and extracted with ether (3 × 20). The ether extract was dried over $MgSO_4$. Solvent removed *in vacuo*. The residue was then subjected to flash chromatography eluting with (50 : 50 EtOAc : pet-ether) to afford the title compound N-carbethoxy-1,2-dihydropyridine **(9a)** and N-carbethoxy-1,4-dihydropyridine **(9b)** as a white oil in the ratio of 72 : 28 (2.31 g, 18%). $R_f = 0.87$ (acetone).

N-Carbethoxy-1,2-dihydropyridine (9a): 1.6 (3H, t, CH_2 CH_3), 4.1 (2H, q, CH_2—CH_3), 4.3 (2H, dd, *J* 4.1, 2.04, 2-H_2), 5.1 (1H, br, 4-H), 5.4 (1H, br, 3-H), 5.85 (1H, m, 5-H), 6.7 (1H, br, 6-H).

N-Carbethoxy-1,4-dihydropyridine (9b): 1.6 (3H, t, CH_2CH_3), 2.8 (2H, m, 4-H_2), 4.1 (2H, q, CH_2 —CH_3), 5.1 (2H, br, 3-H and 5-H), 6.6 (2H, d, *J* 6.3, 2-H). ν_{max}/cm^{-1} 1700 ν(C═O), 1548 ν(C═C), 2980 ν(C—H).

(1′R,S,3′S,R,1R,S,4R,S)-{Spiro-1′,3′-dithiane-2,2′-7-Ethoxycarbonyl-7-aza-bicyclo[2.2.2]-oct-5-ene}-1′,3′-dioxide (10 : 10): (**Scheme-3**) Racemic (1R,S, 3R,S)-2-methylene-1,3-dithiane-1,3-dioxide **(4)** (0.1 g, 0.61 mmol) was dissolved in propionitrile (0.6 mL) and freshly prepared N-ethoxycarbonyl-1,2-

dihydropyridine (0.14 g, 0.91 mmol from mixture of isomer **(9a : 9b)** added. The solution was refluxed for 9 d. The solvent was removed and the residue subjected to flash chromatography eluting with EtOAc : acetone **(50 : 50)**. The title compound was obtained as a brown oil (40 mg, 20%) as a mixture of diastereomers (ratio: 76 : 24). δ_H (250 MHz, $CDCl_3$) 1.2 (3H, t, CH_2CH_3), 1.2 (1H, m, 3-H_a), 2.1 (1H, m, 3-H_b), 2.4 (2H, m, 5′-H_b and 5′-H_a), 2.9 (3H, m, 4′-H_a, 4′-H_b and 6′-H_a), 3.3–3.5 (2H, m, 7-H_a and 6-H_b), 3.6–3.7 (1H, m, 4-H), 4.0 (2H, q, CH_2CH_3), 4.1–4.2 (1H, m, 7′-H_b), 5.2 (1H, dd, *J* 17 and 5.7, 1′-H), 6.6 (2H, dt, CH=CH). m/z (LC-MS): 318.1[M^++(H^+) 93.9%], 317.15 (M^+ 0.2%), 298.3 (17.9), 284.3 (9.5), 270.3 (17.9), 228.20 (19.5), 217.0 (100), 167.0 (13.4), 149.0 (27.8), 102.1 (5.1), 91.1 (31.5). ν_{max}/cm^{-1} 2962 ν(CH), 1684 ν(C=O), 1563 ν(C=C), 1024 ν(S=O).



(4a) (9a) (9b)

Scheme-3

In summary, we have found a convenient method for preparation of the racemic *trans*-(1R,S,3R,S)-2-methylene-1,3-dithiane 1,3-dioxide **(4a)** in three steps and Diels-Alder reaction with N-carbethoxy-1,2-dihydropyridine **(9a)** shows moderate diastereoselectivity (76 : 24) cycloaddition product **(10a : 10b)** in 20% yield.

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